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Local synaptic connections of basal forebrain neurons

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Abstract

Single, biocytin filled neurons in combination with immunocytochemistry and retrograde tracing as well as material with traditional double-immunolabeling were used at the light and electron microscopic levels to study the neural circuitry within the basal forebrain. Cholinergic neurons projecting to the frontal cortex exhibited extensive local collaterals terminating on non-cholinergic, (possible GABAergic) neurons within the basal forebrain. Elaborate axon arbors confined to the basal forebrain region also originated from NPY, somatostatin and other non-cholinergic interneurons. It is proposed that putative interneurons together with local collaterals from projection neurons contribute to regional integrative processing in the basal forebrain that may participate in more selective functions, such as attention and cortical plasticity.

Keywords: Juxtacellular labeling; Cholinergic neurons; GABAergic neurons; Parvalbumin-containing neurons; NPY neurons; EEG

1. Introduction

Comparative anatomical studies [14,45] in the middle of the twentieth century emphasized the progressive development of the peculiar aggregated neurons in the basal forebrain (BF) in the mammalian phylogeny. Nonetheless, this region remained largely a terra incognita or 'unnamed substance' [50,51] even in the 'renaissance' of neuroanatomy beginning in the late sixties. Recent interest in BF research was surged by discoveries in the late seventies and early eighties showing that a specific population of neurons in this region, namely those that use acetylcholine as their transmitter and project to the cerebral cortex, are seriously compromised in Alzheimer's disease (AD) [5,24,44,81,92,93,97]. Moreover, this neuronal damage could be, at least, partially responsible for the deteriorating cognitive functions in AD and related disorders [8,12,23,79].

A combination of single unit recordings in the BF and EEG monitoring [16,25–30,56,72,76] during various behaviors indicated that neocortical activation critically depends on basal forebrain inputs to the cortex. The neural circuitry underlying BF modulation of cortical activity still remained obscure, because these studies did not identify the recorded neurons chemically or morphologically [26]. Basal forebrain areas, including the medial septum/vertical limb of the diagonal band (MS/VDB), horizontal limb of the diagonal band (HDB), sublenticular substantia innominata and pallidal regions (ventral pallidum and globus pallidus) contain a heterogeneous population of neurons, where cholinergic, non-cholinergic projection neurons, and putative interneurons are intermingled along different ascending and descending pathways [111]. In vitro electrophysiological studies [3,57,73] as well as in vivo recordings of single neurons [77], in combination with transmitter identification of the recorded cells, opened the way to determine the specific function of the individual neural elements of the BF [32]. A precise knowledge of input–output relationships of specific neurons, including their local synaptic interactions will address many questions, such as how different neuronal populations of the BF may concurrently participate in generalized (e.g. arousal) or more selective functions, including cortical plasticity and attention (for discussion, see [111]). This review summarizes our preliminary

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studies[1] concerning local axon collaterals of identified BF neurons and their possible postsynaptic targets.

Recent studies in rats suggest that cholinergic neurons make up only about half of the neurons projecting to neocortical areas, the rest contain various calcium-binding proteins [111], including parvalbumin, calretinin and calbindin. Fig. 1 shows the three-dimensional distribution of the two most prevalent basalocortical projection systems: the cholinergic and parvalbumin-containing neurons.

2. Cholinergic neurons

Studies using multiple retrograde tracers or antidromic activation of basalocortical neurons suggested that individual cholinergic axons are highly branched in their cortical terminal fields but seldom collateralize to innervate different parts of the cortex [6,7,64,82]. Our own studies [Csordas and Zaborszky, in preparation] using multiple tracers delivered into functionally related cortical areas tend to support this notion, in contrast to some earlier [1,70], and more recent suggestions [57] that cholinergic or non-cholinergic neurons would provide dispersed collaterals to innervate widespread cortical regions. Using Golgi impregnation or choline acetyl transferase (ChAT) immunostaining [13], only the initial segment (up to 50 μm) of the axons can be observed. Therefore, no data are available about the local arborizations of cholinergic axons. A study using intracellular iontophoresis of HRP for staining of antidromically identified neurons revealed that corticopetal neurons in the BF had local axon collaterals displaying numerous boutons en passant [84,86], however, due to the lack of transmitter identification, the classification of the reconstructed neurons remained open to speculation [26].

Fig. 2 shows the partial reconstruction of a cholinergic neuron in the ventral part of the globus pallidus that projects to the prefrontal cortex. This neuron had several local collaterals arborizing in an area of approximately 0.2 mm^3 and giving rise to about 50 en passant boutons. The bouton shown in Fig. 2F establishes a symmetric apposition with the dendritic shaft of an undetermined neuron. In this material, no evidence was found that cholinergic axons enter into synaptic connections with other cholinergic profiles. Using a database containing four different types of BF neurons [Zaborszky, Buhl, Bjaalie, Poobalashingam and Nadasdy, in preparation], it can be estimated that in the same tissue volume, where this cholinergic neuron distributes axon collaterals, there are about 600–700 other cell bodies, including parvalbuminin (50%), calbindin (25%), other cholinergic (20%), and a few calretinin-containing neurons (5%). Although the neuropil composition of these different cellular profiles is unknown, one can speculate that even without addressing a specific postsynaptic target, cholinergic axons may contact different cell populations with some preference, depending on their differential distribution in the BF [111].

3. Parvalbumin-containing neurons

3.1. Globus pallidus

The cholinergic forebrain areas, including the globus pallidus, internal capsule and HDB contain numerous parvalbumin (PV)-positive neurons (Fig. 1). Most of the PV-positive neurons in pallidal areas are projection neurons, innervating the striatum [66], the thalamus and substantia nigra [83]. Fig. 3 shows a partially reconstructed PV neuron in the globus pallidus that discharged in a regular firing pattern with a mean firing rate of 40 Hz. This neuron was characterized by mildly varicose, smooth dendrites, and an often-rectangular dendritic branching pattern. Spines were rarely observed. The main axon was followed several mm in a descending course in the internal capsule passing through the entopeduncular nucleus. A larger collateral, shown in Fig. 3D, gave rise to several boutons in the globus pallidus and was traced as far as the striatum. One of the PV-positive boutons in the globus pallidus entered into an asymmetric synaptic contact with a medium-sized, longitudinally sectioned dendrite (Fig. 3F). Due to absence of the characteristic 'palisade like' [34], arrangement of synaptic sheets along this dendrite and the presence of flocculent immunoprecipitate in this dendrite from adjacent sections, we tentatively suggest that this profile may belong to a cholinergic neuron. A previous study [61] extensively characterized PV neurons in the globus pallidus at the

[1] Anesthetized (urethane, i.p. 1.2 g/kg) adult male Sprague–Dawley rats were given 0.2 μl pressure injections of Fluoro Gold (5% in dd H_2O) into the frontal cortex. After 6 days the animals were re-anesthetized and extracellular recordings were obtained from neurons in the BF. Following extracellular recordings neurons were juxtacellularly stained with biocytin as described earlier [77]. After perfusion and sectioning, the biocytin filled neurons were visualized using avidin-conjugated Lissamine Rhodamine (LR) fluorescent labeling. The biocytin stained neurons were then sequentially stained for the presence of choline acetyltransferase followed by parvalbumin. The LR-positive somas were then developed for light microscopy using the Ni enhanced ABC/DAB protocol. Finally, sections were processed using an additional ChAT immunostaining and embedded into plastic for subsequent electron microscopic investigation of putative synaptic contacts. Drawings and micrographs of Figs. 6–8 are from the same material as presented in a previous review [101]. All procedures were carried out in strict accordance with guidelines set forth in the PHS manual 'Guide for the Use and Care of Laboratory Animals'.

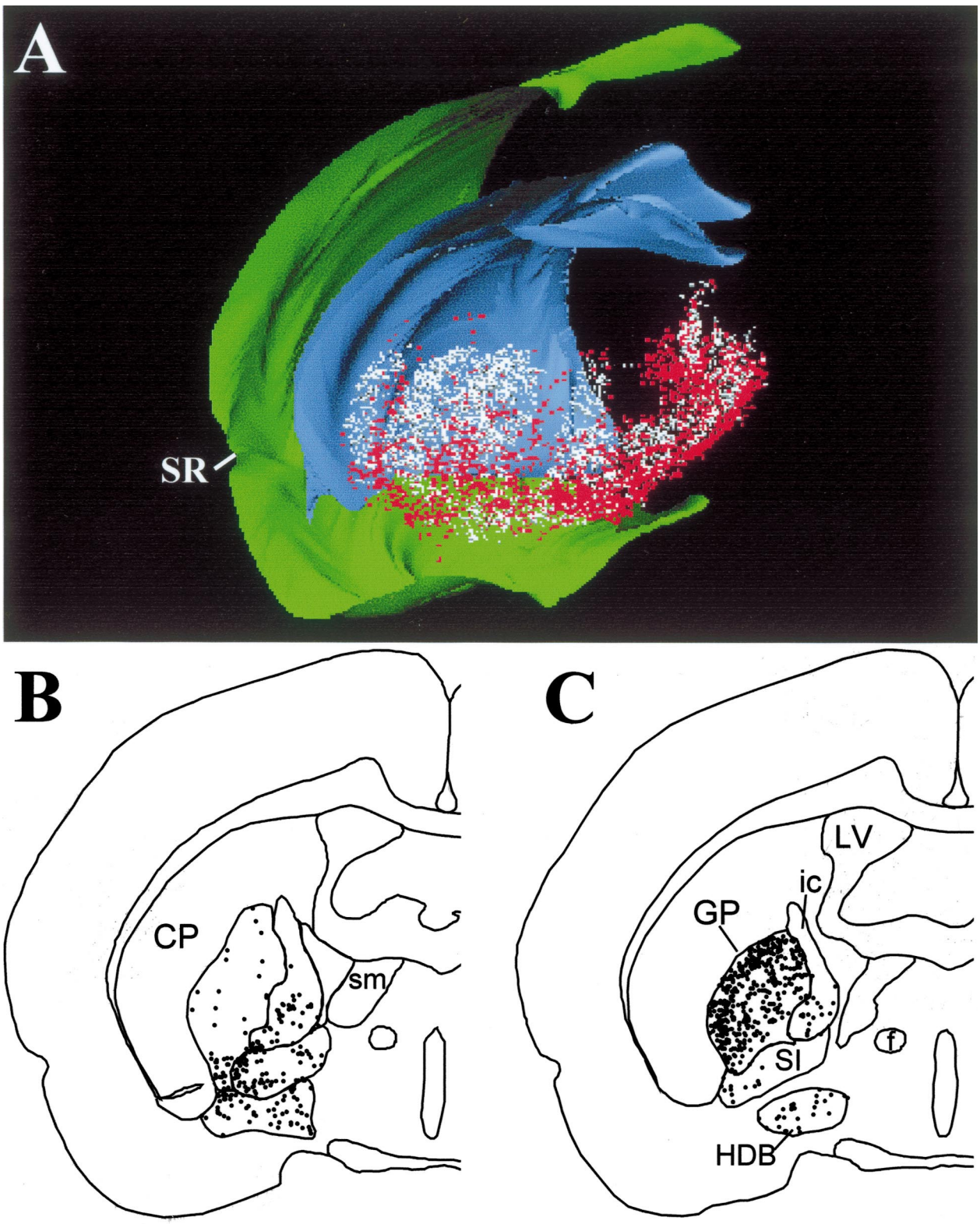

Fig. 1. Distribution of cholinergic and parvalbumin-containing neurons in the basal forebrain. (A) Neurons from alternate sections stained for choline acetyltransferase (ChAT: red) and parvalbumin (PV: white) were mapped using the Neurolucida® (Microbrightfield) software. Data were then converted into the Micro3D® (Oslo Research Park) software and visualized using an SGI computer for 3-dimensional rendering. Note that both cell types show higher and lower density regions (clusters) and the two markers change their medio-lateral position from rostral to caudal. The corpus callosum is visualized in blue, the outline of the brain in green. (B and C) Two sections (approximately 300 μm apart) from a series stained for ChAT (B) and PV (C), respectively. Abbreviations: CP, caudate putamen; f, fornix; GP, globus pallidus; HDB, horizontal limb of the diagonal band; ic, internal capsule; LV, lateral ventricle; SI, substantia innominata; sm, stria medullaris; SR, rhinal sulcus.

electron microscope level. According to that study most of the PV-positive boutons in the globus pallidus (86%) formed symmetric synapses with somata and large dendrites, while the remaining 14% formed asymmetric synapses with medium to small dendrites. However, the above study was not able to determine whether PV-positive terminals in the globus pallidus originate from local axon collaterals of PV-positive pallidal neurons or derive from an outside afferent source. According to the same study, many of the postsynaptic targets of PV-boutons were also PV-positive neurons; however, some PV-positive boutons were seen in contact with unlabeled dendritic profiles, similar to what is shown in Fig. 3. F. Bevan et al. [10] reconstructed several pal-

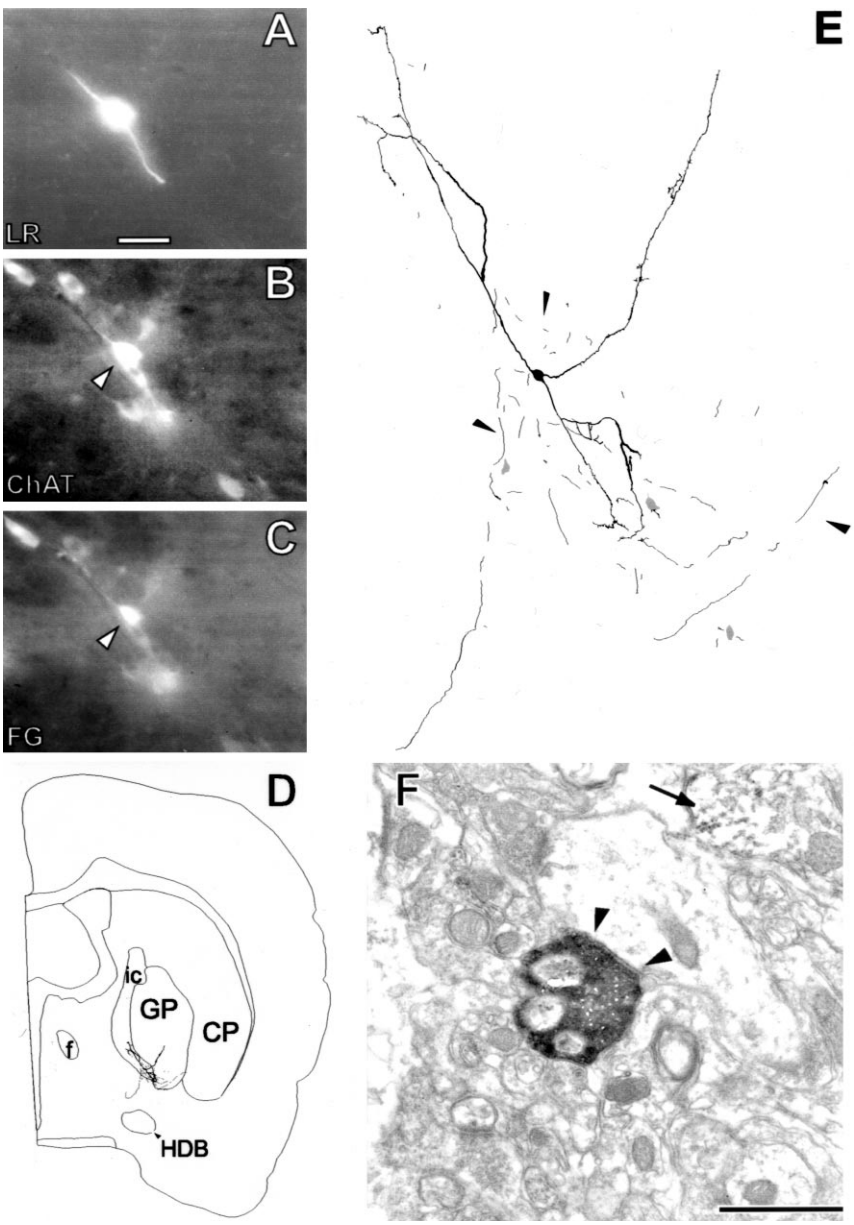

Fig. 2. Partial reconstruction of a juxtacellularly filled cholinergic neuron. (A) Visualization of the biocytin injected neuron using Lyssamine Rhodamine (LR) fluorescent marker. (B) Arrowhead points to the same neuron as filled with biocytin in (A) is stained for the presence of choline acetyl transferase (ChAT) using FITC labeled secondary antibodies. (C) The same neuron is also retrogradely labeled with Fluoro-Gold (FG) delivered into the frontal cortex a week prior of the recording session. (D) Diagram illustrating the location of the reconstructed neuron. (E) High magnification view of the reconstructed cholinergic neuron. Arrowheads point to various segments of the axon. Note that the area around the cell body is rich in axon collaterals but the varicosities present are extremely fine and not visible at this magnification. The three stippled symbols represent other cholinergic cell bodies that were adjacent to labeled boutons without synaptic contacts. (F) Electron micrograph showing that a biocytin filled profile is in symmetric synaptic contact with an unlabeled dendrite. Arrow points to another dendrite containing flocculent immunoprecipitates indicative of ChAT in this dendritic profile. Bar scale: 1 μm in (F) and 50 μm in (A). Abbreviations: see Fig. 1. Neurons depicted in this and subsequent figures were reconstructed using the Neurolucida® software package. The files were then edited applying Adobe® Illustrator 8.0.

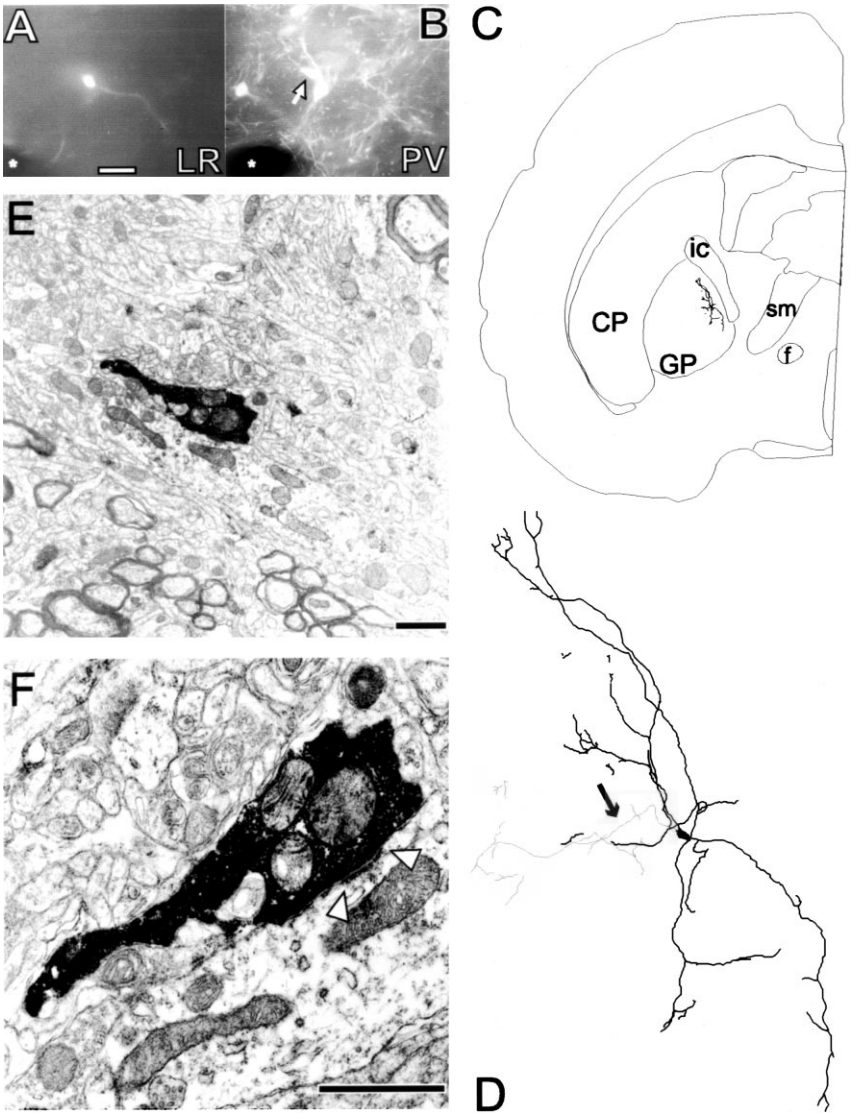

Fig. 3. (A–B) Arrow points in (B) to a neuron positive for parvalbumin (PV) that was filled with biocytin and labeled with Lyssamine Rhodamine (LR) in (A). (C) Schematic drawing showing the location of the reconstructed neuron. (D) High magnification view of the reconstructed neuron. Dendrites are indicated by heavy lines, axons with fine lines. Note the dendrites are smooth and their endings show often claw-like complex processes. Arrow points to a region, from where the synaptic contact depicted in (E–F) are taken. (E) Low magnification electron micrograph showing a labeled elongated axonal process in close contact with a dendrite. Note this dendrite contains some flocculent diamino benzidin product, representing choline acetyl transferase immunostaining and there are very few other terminal boutons around this dendrite. The lower left half of this micrograph contains several myelinated fibers of the internal capsule. (F) High magnification micrograph showing that the biocytin labeled axonal profile enters into an asymmetric synaptic contact (arrowheads toward the postsynaptic thickening) with the dendrite. Bar scale: 1 μm in E, F and 50 μm in A. Abbreviations, see Fig. 1.

lidostrial neurons that were characterized by variable amount of spines and complex varicose dendritic endings on some of the tertiary dendrites. Due to the fact that the pallidostriatal neurons in the study of Bevan et al. [10] were not tested for the presence of PV, it is unclear, whether or not the cell shown in Fig. 3 represents the same or a different type of pallidal neuron. Since the pallidostriatal projection is in register with that of the striatopallidal projection [10,62] and cholinergic neurons in pallidal areas seem to receive topographically organized input from striatal areas [53,104], it is possible that cholinergic, PV-containing neurons in pallidal areas and specific GABAergic striatopallidal neurons participate in short basal ganglia feedback loops, the function of which is still undetermined. Since the PV neuron in Fig. 3 did not contain the retrograde tracer applied in the frontal cortex, it remains to be elucidated whether or not globus pallidus PV neurons project to the cerebral cortex.

3.2. Septum-diagonal band

Many PV cells in the septum and HDB project to the hippocampus [35] and cerebral cortex [111], respec-

tively. PV has been found in GABAergic neurons in many brain areas, including GABAergic local neurons of the cerebral cortex, the hippocampus, and the neostriatum [17,20,63,65]. Identified PV cells in the BF discharged at 7–15 Hz, regular or in random modes and showed positive correlation in their discharge pattern to concurrent EEG desynchronization (Duque, Balatoni, Detari and Zaborszky, in press). Since GABAergic basalocortical axons were found to terminate exclusively on cortical GABAergic interneurons [37], our finding is compatible with the notion that GABAergic basalocortical input promotes functional activation in the cerebral cortex by disinhibition [56].

4. Other non-cholinergic projection neurons

Fig. 4 shows a retrogradely labeled, juxtacellularly filled neuron in the anterior amygdaloid area that projected to the prefrontal cortex. This neuron was tested for the presence for ChAT and for two calcium-binding proteins, PV and calretinin. None of these substances turned out to be localized within this neuron. A partial

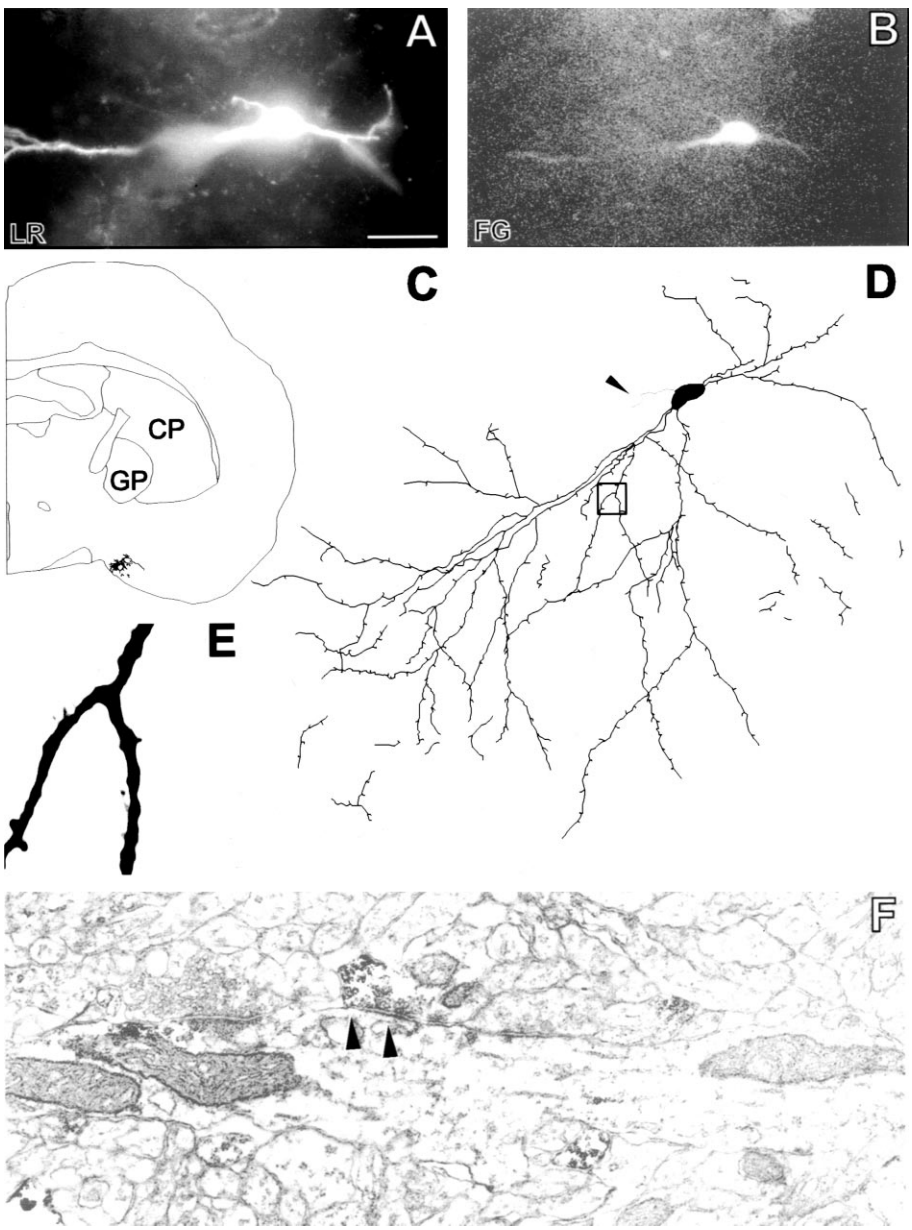

Fig. 4. (A–B) biocytin filled neuron marked with Lyssamine Rhodamine (LR) in (A) that is also retrogradely labeled from the frontal cortex using Fluoro-Gold (FG) in (B). (C) Shows the location of this neuron in the anterior amygdaloid area. (D) High magnification view of the neuron. Note the richly arborized denritic processes that are heavily studded with spines. Arrowhead points to the origin of the axon. (E) Higher magnification view of the boxed area in D. (F) High magnification electron micrograph showing a longitudinally cut dendrite that is contacted by a biocytin filled axon terminal. Arrowheads point to the symmetric postsynaptic side. Bar scale, 1 μm in (F) and 50 μm in (A). Abbreviations: see Fig. 1.

reconstruction of this neuron revealed that the dendrites were studded densely with spines and had a few initial axon collaterals with en passant varicosities. Morphologically this neuron is very similar to the corticopetal cell # 2 in the paper of Semba et al. [86] that was located in the same general area of the BF. Fig. 4F shows one of the local boutons establishing a symmetric synapse with an unlabeled dendrite. According to our electrophysiological characterization, this neuron had an extremely slow firing rate. The neuron in the study of Reiner et al. [84] and Semba et al. [86] showed loss of the somatodendritic segment of the antidromic action potential following high frequency stimulation, and it was tentatively suggested to be a non-cholinergic neuron. Failure of somatic spike has been found in monoaminergic neurons bearing autoreceptors [49], as well as motoneurons known to have local negative feedback mechanisms [19].

In our preliminary studies, we found several morphologically distinct types of non-cholinergic, PV-negative projection neurons with few or no local collaterals that were also negative for calbindin or calretinin. At

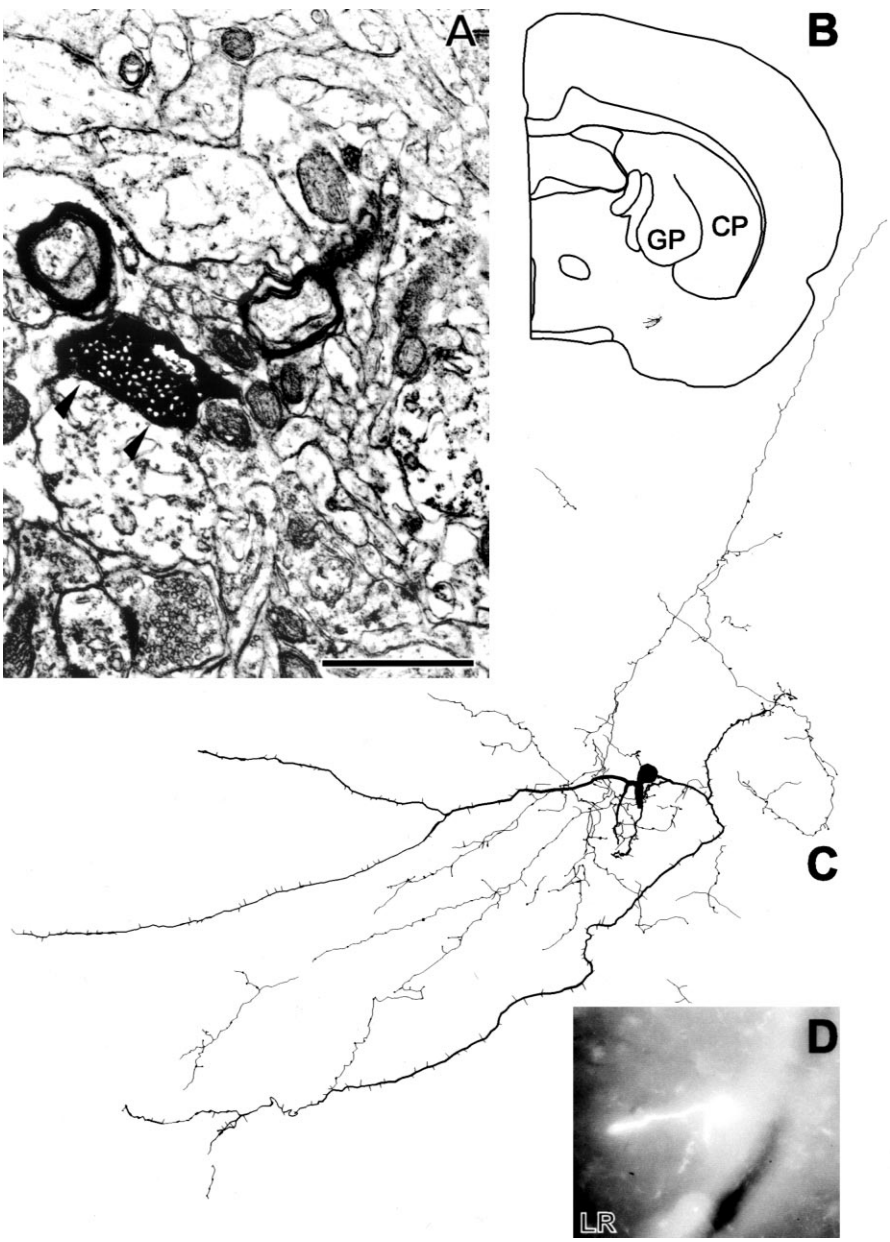

Fig. 5. A neuron in the horizontal limb of the diagonal band that was negative for parvalbumin and choline acetyl transferase. (A) High magnification electron micrograph of a biocytin-filled axon terminal of this neuron entering into symmetric contact with a dendritic shaft of undetermined origin. Arrowheads point to postsynaptic membrane thickenings. (B) Schematic drawing indicating the location of this neuron. (C) High magnification view of the reconstructed neuron. Note the presence of spines and a few complex endings on the dendrites. A very extensive local collateral network occupies the area of the dendritic field. The axons bear numerous large varicosities. (D) Photomicrograph of the lissamine rhodamine containing neuron. The black archiform shadow corresponds to a vessel. Bar scale in A, 1 μm.

present, it is unclear what type of neurotransmitter is in these non-cholinergic corticopetal neurons and what is their local and/or cortical postsynaptic target.

5. Putative local circuit neurons

Fig. 5 shows a sparsely spiny neuron that was negative for ChAT and PV and is partially reconstructed. Around the cell body and occupying a large part of the dendritic arbor, a dense network of axon collaterals can be seen. These collaterals bear numerous large, bulbous varicosities. Within a space of about 0.14 mm^3, 374 varicosities were counted. Within this axonal arborization volume, there are about 550 other neurons, including 300 calretinin, 200 cholinergic, 40 parvalbumin and 10 calbindin-containing cells. One of the axonal varicosities shown in Fig. 5A enters into symmetric synapse with a dendritic shaft. The chemical characteristics of this postsynaptic profile have not been determined.

Somatostatin is found in axon terminals in contact with cholinergic neurons in the substantia innominata [101]. The synapses observed were of the symmetric type and were found primarily on proximal dendrites or on cell bodies. The result of a high magnification light microscopic mapping of the axonal arborizations of somatostatin neurons in the BF using a double-labeling protocol (Fig. 6) suggest that somatostatin axons indiscriminately surround cholinergic (stippled in this figure) and non-cholinergic neurons. Based upon analysis of single sections, it is apparent that one somatostatin neuron can innervate as many as five–10 cholinergic neurons and perhaps several somatostatin neurons can contribute collaterals to one cholinergic neuron. Unfortunately, due to the difficulty in such double-labeled material to trace axonal processes back to their parent cell bodies, it is unclear whether distant projections also contribute to the somatostatinergic innervation of cholinergic neurons. It is apparent, however, that the density of local somatostatin neurons in the various BF regions is different, [Zaborszky and Hajszan, in preparation]; therefore, it is possible, that cholinergic neurons are subject to varying degrees of local somatostatinergic influence. Somatostatin containing neurons have been reported to contain GABA and represent a specific type of interneuron in the hippocampus [58]. Also, somatostatin has been reported to inhibit acetylcholine release from cholinergic neurons of the myenteric plexus [100]. The functional significance of somatostatin/cholinergic interaction in the BF remains to be elucidated.

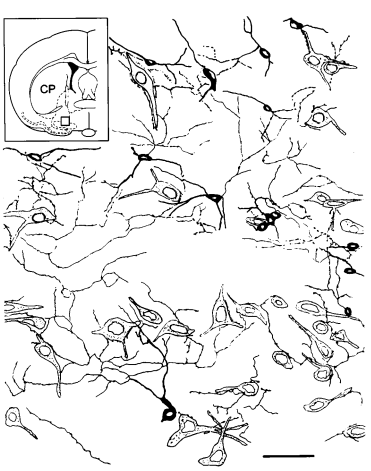

Fig. 6. Distribution of axon collaterals of local somatostatin-containing (S) neurons among cholinergic neurons from the area indicated by the box in the upper left inset. To prepare the inset, we used Fig. 20 from the atlas of Paxinos and Watson [78]. Cholinergic cells are stippled, S cell bodies marked with jet black. Note that one somatostatin axon provide collaterals to several cholinergic cell bodies, but S axon terminals containing varicosities are localized also in areas devoid of cholinergic profiles. This drawing was prepared using a section processed for choline acytltransferase and somatostatin, using a double-label protocol. Abbreviations: CP, caudate putamen. Scale bar, 50 μm.

Neuropeptide Y (NPY) containing terminals in the BF contact cholinergic projection neurons. NPY-positive fibers and terminals were found to surround cholinergic neurons in the lateral part of the medial septal nucleus, dorsal part of the HDB and the substantia innominata, similar to the distribution of somatostatin-containing fibers [101]. Cholinergic cell bodies are often ensheathed by NPY-containing terminals which could be followed to local NPY neurons. Fig. 7 shows in the lateral part of the HDB, near the substriatal gray, two NPY-containing neurons. Their bifurcating axons could be followed to the cholinergic neuron seen in the lower left part of this figure. Single NPY neurons can innervate several cholinergic neurons. Using a correlated light-EM double labeling technique (Fig. 8), NPY-containing terminals in the substantia innominata can be seen to enter into symmetric synapses with the cell bodies and proximal dendrites of cholinergic neurons. Similarly, Tamiya et al. [94] found synaptic contacts between NPY-immunoreactive fibers and cholinergic neurons in the HDB. With juxtacellular labeling, where single axonal arborization can be studied in more detail, we estimated (Duque and Zaborszky, in preparation) that single NPY neurons may give rise to as many as 600 boutons in the dendritic field of the parent neurons.

No electrophysiological study examined the putative NPY/cholinergic interaction in the basal forebrain. According to our preliminary study (Duque, Balatoni, Detari and Zaborszky, in press), NPY-positive neurons in the BF are silent during spontaneous or tail pinch induced desynchronization, but accelerated during episodes of cortical delta oscillations. The lower part of Fig. 9 shows a hypothetical cholinergic neuron, receiving several different types of axon terminals, including NPY-containing boutons. The upper part of this figure

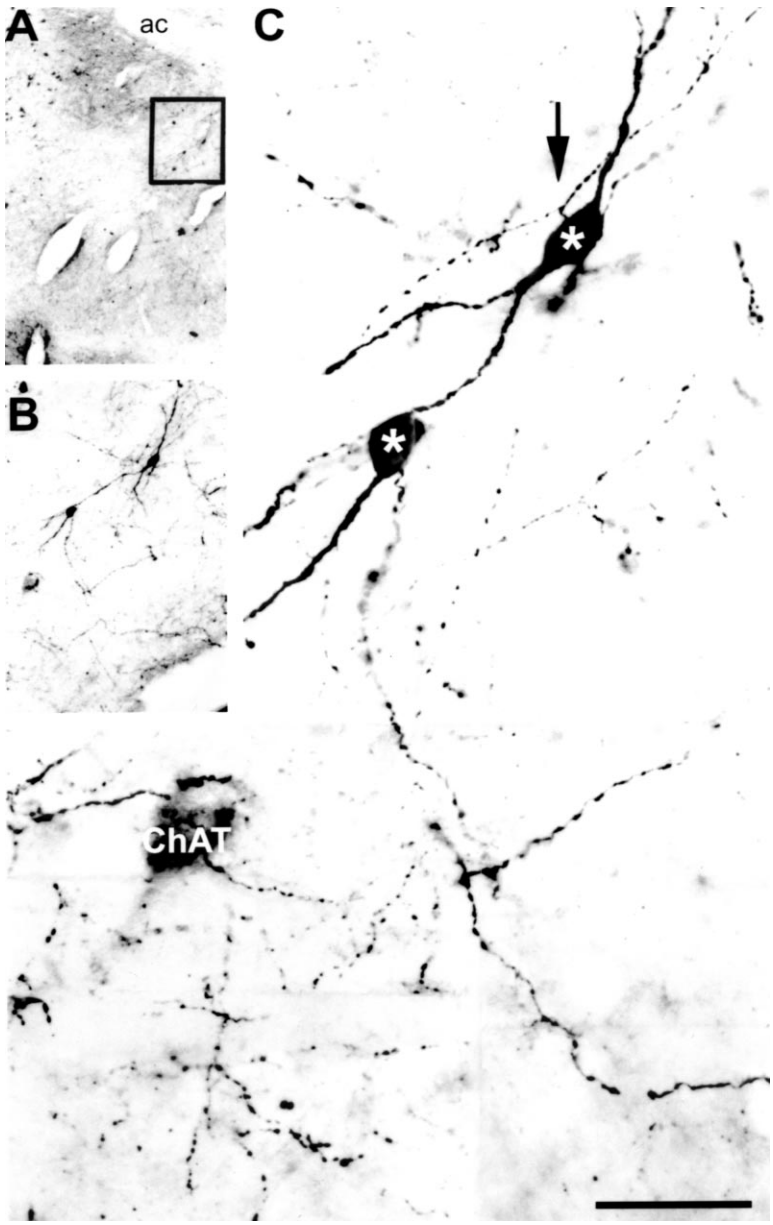

Fig. 7. NPY/cholinergic interaction in the basal forebrain. (A) Low magnification photomicrograph, showing the location of some cells underneath the anterior commissure (ac). (B) Low magnification photomicrograph from the boxed area of (A). (C) High magnification photomontage of the boxed area in (A) showing two NPY-positive neurons in the upper right (black fusiform cell bodies marked asterisks) with their bifurcating axon collaterals (large arrow) surrounding the cholinergic cell body (ChAT) seen in the lower left corner. These photomicrographs were taken from a section processed for choline acetyltransferase and NPY using NiDAB for NPY and DAB for labeling cholinergic neurons. Bar scale: 50 μm.

schematically illustrates that a barrage of spikes of the NPY neuron in slow-wave sleep may be coincident with quiescence in synaptically connected cholinergic neurons.

NPY is a potent anxiolytic agent. Intracerebroventricular administration in awake rats produces slowing of delta activity and reduces the auditory N1 component of the event related potentials (ERP) in the frontal cortex in an 'oddball' paradigm [33]. NPY also produced a reduction in the P3 component of the ERP in the amygdala [33]. The N1 and P3 components of the ERP have been suggested to reflect attention and stimulus evaluation, respectively [55]. The P3 component disappears following BF lesion in rabbits [96] and Y1 receptor agonists produce similar EEG changes that have been reported after administration of benzodiazepines [33], compounds that act partially via the basal forebrain [75]. NPY has been found to coexist with GABA in many forebrain neurons [4]. Taken together, these data with NPY synapses on cholinergic neurons and data on discharge properties of NPY neurons as they relate to EEG epochs raise the possibility that the BF represents a brain site responsible for NPY's anxyolitic actions.

6. General discussion

Understanding of the cellular organization of the cerebral cortex, including the hippocampus, has advanced in the last twenty years primarily due to the application of intracellular electrophysiology with rigorous combination of correlated light and electron microscopic techniques [15,36,40,48,88]. Such methods, for technical reasons, were not adapted in their full capacity in the BF [67,84,86]. More recently, the application of the juxtacellular technique of Pinault [77,80] with a combination of immunostaining to identify the transmitter content of the recorded neurons began to unravel the functional circuitry of the BF. The integrative capacity of the cerebral cortex largely depends on the presence of various types of inhibitory and excita-

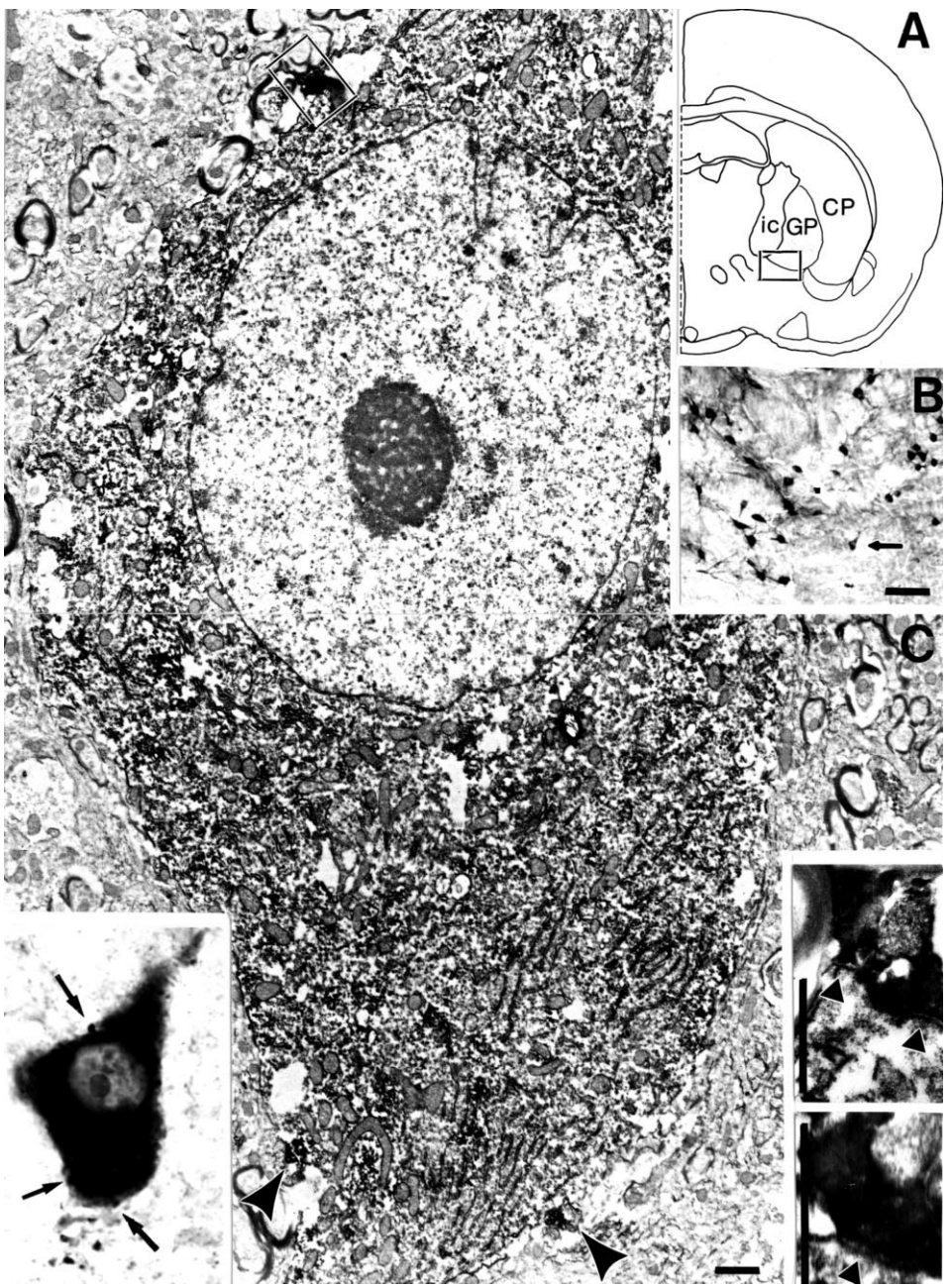

Fig. 8. NPY/cholinergic interaction in the basal forebrain. (A) Schematic drawing showing the location of the cholinergic neuron in the substantial innominata (arrow in B) that was subsequently investigated with electron microscopy to identify synaptic contacts. (C) low magnification electron micrograph of a cholinergic neuron. Note the presence of heavy immunostaining in the perikaryon which is also rich in endoplasmic reticulum, characteristic for cholinergic projection neurons. Several NPY containing varicosities approaching the cell body are labeled by arrowheads. The bouton enclosed in the box at upper left to the cell body is enlarged in the two insets at lower right, which are taken from two adjacent thin sections. Arrowheads in these insets point to the postsynaptic membrane thickening. Bar scale in the inset 1 μm; in B, 100 μm.

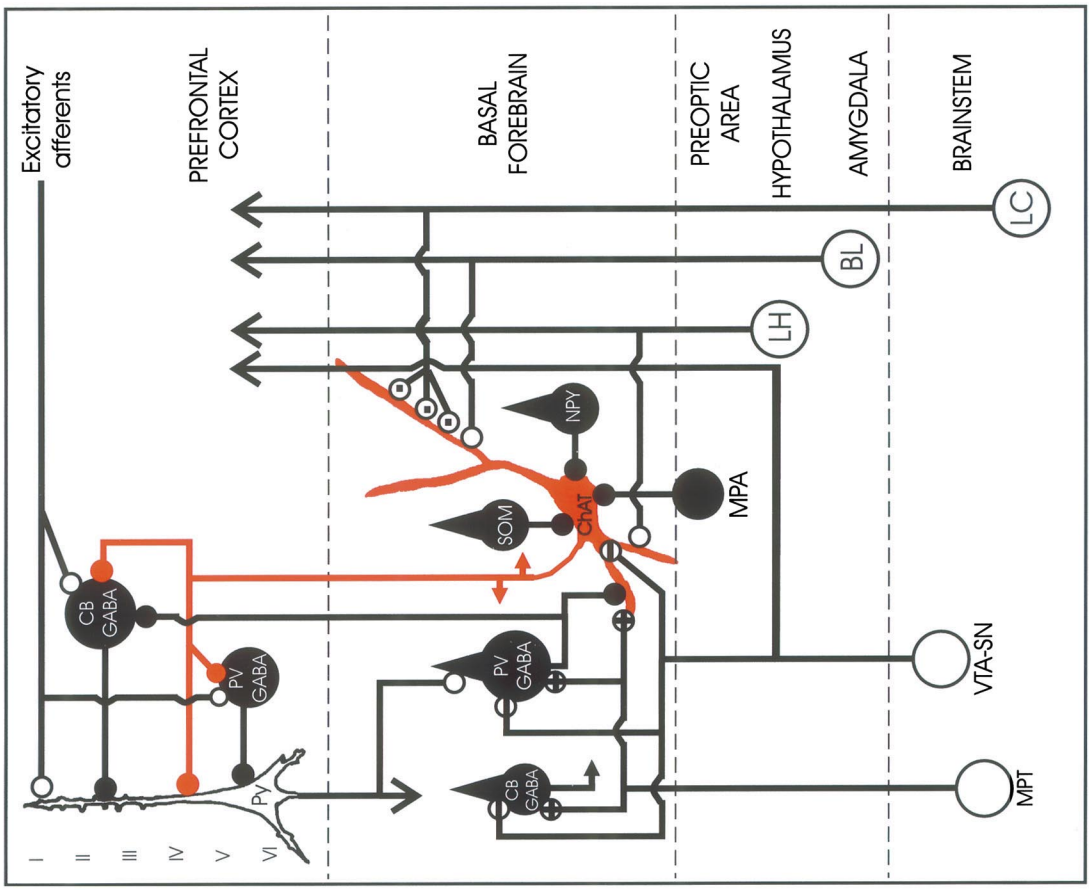
Excitatory afferents
PREFRONTAL CORTEX
BASAL FOREBRAIN
PREOPTIC AREA
HYPOTHALAMUS
AMYGDALA
BRAINSTEM
I
II
III
IV
V
VI
CB GABA
PV GABA
PY
SOM
NPY
ChAT
MPA
LH
BL
LC
VTA-SN
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Fig. 10

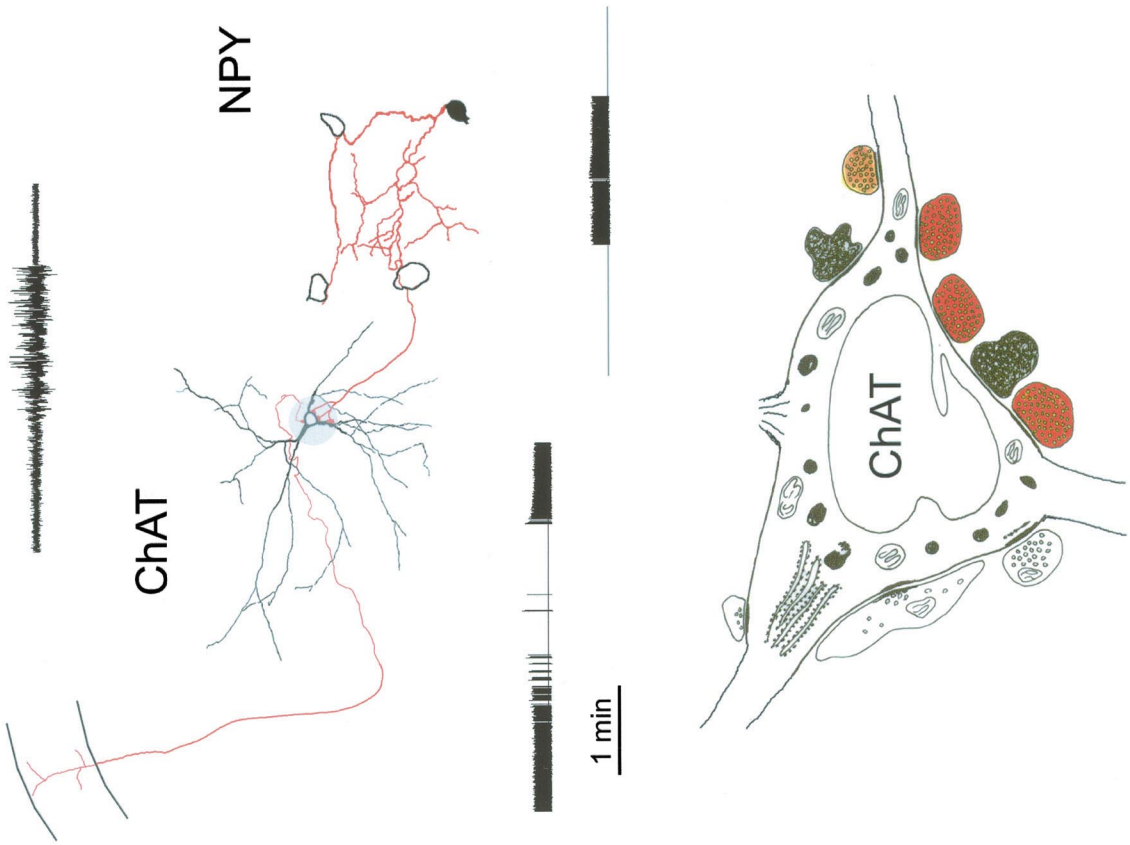
ChAT
NPY
1 min
ChAT

Fig. 9

Fig. 9. Putative functional circuit in the BF. The lower half of this figure contain a hypothetical cholinergic neuron that is identified based upon the presence of large HRP granules as projecting to a certain cortical area and receiving various type of boutons to its perykarion. Red color marks NPY-containing boutons, black and yellow symbolize for example GABAergic and substance P-containing boutons (for the various synapses identified on cholinergic neurons see [102]). The upper part of this figure shows an NPY-containing neuron (black) that innervate several cholinergic neurons (marked with heavy outlines), including the one in the middle that is fully reconstructed with its dendritic arbor. Assuming that both neurons are recorded simultaneously (left and right traces in the middle) in vivo, one can establish the correlation of the firing rates of these interconnected neurons with fast and slow epochs in the EEG (top of this figure).

Fig. 10. Schematic diagram illustrating the mode of termination of different afferents on corticopetal cholinergic (ChAT, red) and other (black) neurons of the basal forebrain. Only those neurons and connections are included here that have been cross-correlated on the basis of fine structural, tracing and/or immunocytochemical identification of the same elements. Note that afferents to cholinergic neurons selectively innervate different portions of the neuron. Amygdala axons from the basolateral amygdala (BL) [110], noradrenergic axons from the locus coeruleus (LC) [105,107] and lateral hypothalamic (LH) axons [22,103] terminate on distal dendrites. Somatostatin, NPY [101], GABAergic [109], medial preoptic (MPA) [22] and dopaminergic [42] axons innervate predominantly the cell body and proximal dendrites of cholinergic neurons. Corticofugal axons terminate on dendritic shafts of parvalbumin-containing neurons [108]. Parvalbumin-containing neurons also receive on their soma dopaminergic input from the ventral tegmental area-substantia nigra (VTA-SN) [43]. The input from parvalbumin cells to cholinergic neurons has been shown in this paper. Parvalbumin [111], calbindin and cholinergic neurons receive also input from the mesopontine tegmentum (MPT) [Kallo and Zaborszky, in preparation]. Inhibitory neurons and their synapses are drawn in full black, excitatory neurons with open symbols. Within the open symbols a minus sign represent dopaminergic synapse, a + sign indicate putative glutamatergic/cholinergic input originating from the MPT [68] and a dot marks a noradrenergic synapse. Input to cholinergic neurons from the ventral [104] and dorsal striatum [53] are not incorporated into this diagram. Substance P [11], enkephalin [18,69] and galanin-containing synapses [54] have been described on BF cholinergic neurons, the precise origin of these terminals, however, is not known. Data are based on studies of the rodent basalocortical neurons; the presence of catecholaminergic and GABAergic synapses on cholinergic neurons of the nucleus basalis in primates has been recently confirmed [90,91]. The highly simpflied data on the intracortical circuitry are from the studies of Gulyas et al. [47], Freund and Meskenaite [37], Beaulieu and Somogyi [9] and Gabbot and Bacon [39].

tory local circuit neurons that address with often remarkable specificity projection or other local neurons. According to our preliminary studies, non-cholinergic projection neurons seem to have sparse-to-moderate local collaterals. On the other hand, cholinergic, NPY, and some other interneurons with unidentified transmitter via their rich local axon collaterals may significantly impact on local processing in the BF. According to in vitro studies, cholinergic and GABAergic cells in the BF display robust intrinsic pacemaker mechanisms which allow them to discharge in rhythmic trains [3]. It has been hypothesized that ligand- or voltage-dependent oscillations of interneurons via GABAergic synapses may be critical for cooperative ensemble function of the hippocampus [88]. Whether local synaptic interactions in the basal forebrain contribute to synchronized activity in BF neuronal populations remains to be elucidated.

In the absence of precise cellular data on synaptic distributions and correlated in vitro recording, we do not know under what conditions these putative interneurons are active and how their inputs affect action potential generation in cholinergic and GABAergic projection neurons. Using bundles of microwires in the BF of cats, under chloralose anesthesia, Detari et al. [29] registered different types of synaptic interactions, including inhibition and excitation. The distance between two units that were in inhibitory relationship often reached as long as 2 mm [Detari, personal communication]. At present, it is unknown whether state-related modulatory inputs (noradrenaline, serotonin) innervate NPY or other local neurons; however, a neuron like the one depicted in Fig. 5 would be in a strategically excellent position to distribute and amplify such modulatory input to a basal forebrain tissue 'block' containing at least 600–800 cells.

The wire diagram of Fig. 10 depicts the complicated array of local and projection neurons in the BF with their major afferent sources and their potential cortical target. Our preliminary studies did not allow us to draw a firm conclusion as to whether the local collaterals address different neurons randomly, or with some specificity. Also, it is unknown whether or not they contact strategically different portions of their target cells. Therefore, the connections involving locally, arborizing axons shown in Fig. 10 should be regarded as an initial attempt at summarizing available data. On the other hand, a considerable amount of evidence exists regarding the synaptic topography of long-range afferents to cholinergic neurons, which are included in this schematic circuit diagram.

This complicated local circuitry is paralleled by a similar complex receptor mechanism. For example, GABA elicits via $GABA_A$ receptors Cl^- dependent postsynaptic currents in cultured basal forebrain neurons [2] and basal forebrain $GABA_A$ receptors are involved in behavior-induced acetylcholine release in the cortex, including the hippocampus [74,85]. In addition, in situ hybridization and immunocytochemical studies suggest that various BF neurons express $GABA_A$ receptors with different subunit compositions: cholinergic neurons are typically characterized by the subunit composition $\alpha3/\beta2,3/\gamma2$, whereas most of the parvalbumin-positive GABAergic neurons express either $\alpha1/\beta2/\gamma2$ or composition $\alpha1/\alpha3/\beta2/\gamma2$ [31,38, 41,52,98]. $GABA_B$ receptors have been localized in the BF of pigeons [95]. Its cellular localization in rodents is unknown, and, consequently, its function remains speculative [2]. Acetylcholine elicits depolarizing or hyperpolarizing responses in different, locally arborizing postsynaptic neurons via nicotinic and muscarinic receptors as has been shown in cortical slice preparations [71,99]. Since muscarinic and nicotinic receptors have been localized in BF, acetylcholine may have a complex effect in local processing similar to its effect in cortical information processing [21,46,57,59,60,89].

Although noradrenergic and dopaminergic axons contact cholinergic neurons in extensive portions of the BF [42,105], the majority of afferents, including cortical, striatal, hypothalamic, and various peptidergic fibers, appear to have a preferential distribution to different regions of the BF [22,53,87,106]. In addition, we have shown recently that prefrontal axons within their distribution area exclusively contact non-cholinergic neurons of the BF, including parvalbumin-containing and other undetermined cell populations [108]. Since the number of putative GABAergic inputs to cholinergic cell bodies varies between different regions in the BF [102] and cholinergic dendrites show marked regionally specific orientation (Zaborszky, Nadasdy and J. Somogyi, in preparation), it is likely that cholinergic neurons process different types of information according to their location in the BF. Preliminary data presented in this paper suggest that collaterals of projection or local circuit neurons could contact only a limited number of specific neurons, depending on the particular location. To what extent local circuit neurons and collaterals of projection neurons together with the more restricted type of afferents mentioned above contribute to regionally specific information processing in the basal forebrain remains to be investigated in future studies.

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